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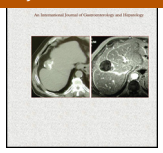

Review Article

Sofosbuvir as backbone of interferon free treatments

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ABSTRACT

Sofosbuvir is the first-in-class NS5B nucleotide analogues to be launched for hepatitis C virus (HCV) treatment. Its viral potency, pangenotypic activity and high barrier to resistance make it the ideal candidate to become a backbone for several IFN-free regimens. Recent data demonstrated that sofosbuvir either with ribavirin alone or in combination with other direct-acting antivirals (DAAs) as daclatasvir, ledipasvir or simeprevir are able to cure HCV in at least 90% or over of patients. Treatment experienced genotype 3 population may remain the most difficult to treat population, but ongoing DAA combination studies will help to fill this gap. Safety profile of sofosbuvir or combination with other DAAs is good. Resistance to sofosbuvir did not appear as a significant issue. The rationale for using this class of drug and the available clinical data are reviewed.

Treatment of hepatitis C virus (HCV) infection has improved dramatically in the last four years. The launch of the first direct acting antiviral (DAA) agents in 2011, boceprevir and telaprevir, first generation protease inhibitors (PIs), in combination with pegylated interferon and ribavirin (PR) was a major step forward in improving HCV treatment [1–6]. However, this progress was hampered by setbacks from toxicity to resistance [7]. In 2014, three new DAAs were approved and launched in a number of Western countries. Sofosbuvir is the first-in-class, potent nucleotide analogue (NA) polymerase inhibitor which acts as a chain terminator within the catalytic site of the NS5B polymerase. FDA and EMA have approved sofosbuvir for pangenotypic HCV treatment either in combination with PR or in IFN-free combinations either with ribavirin or other DAAs. Simeprevir is a second wave first generation NS3/4A PI with potent antiviral activity in genotype 1, 2, 4, 5 and 6. FDA and EMA have approved this agent as part of a combination therapy for naïve or treatment experienced genotype 1 patients and also allows its use in combination with other DAAs. Daclatasvir is a potent first-in-class NS5A inhibitor that has been shown to have a pangenotypic activity. EMA has validated the use of daclatasvir in combination with other agents including sofosbuvir for the treatment of chronic hepatitis C. Moreover, a large number of DAA-based regimens are in the late stage of clinical development and others are in the pipeline [7,8]. This new step forward demonstrates that IFN-free DAA regimens with a shortened duration of treatment are able to improve sustained virological response (SVR) rate to over 90%, thus raising the possibility of curing HCV.

1. IFN-free DAAs-based regimen, is a backbone needed?

The better understanding of the viral life cycle has allowed the development of DAAs targeting different parts of the viral genome [9]. These novel agents inhibit the virus more potently than interferon but are able to generate more or less rapidly resistant variants with continuous treatment [10]. With single-drug treatment, a resistant variant with good fitness may outgrow the wild-type virus within a few days and become the predominant viral species in the population thus leading to treatment failure. The first approach in dealing with DAA resistance was to associate DAAs with PR. Peg interferon stimulates a host of genes, known as interferon-stimulated genes, which have antiviral activities and constitute an effective backbone to prevent the development of DAA resistance especially if the DAA's antiviral potency is high [11].

When moving to IFN-free regimens we may need a new backbone with a high barrier to resistance and potent antiviral efficacy in order to use this compound with only one other class of DAAs, thus reducing drug–drug interactions and allowing short treatment duration. An alternative to a backbone is the use of an association of

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multiple low barriers to resistance and antiviral potent DAAs. This effective strategy is, however, currently limited to genotype 1 and 4 patients [12–17].

The barrier to resistance may be either genetic such that more than one nucleotide change is needed for resistance to emerge; it may be due to high drug exposures that inhibit low-level resistant virus or it may be related to the poor fitness of the resistant variant. Therefore, a high barrier to resistance is needed for any DAA to become a backbone for HCV treatment [18].

Among the different classes of DAAs, NA NS5B polymerase inhibitors appear to be the preferred backbones for IFN-free treatment. This is due to the fact that the most common resistant variant for NA NS5B polymerase inhibitors is a substitution of serine to threonine at position 282 (S282T) in the active site of the RNA-dependant RNA polymerase (RdRp). However, this variant is extremely unfit with an 11-fold reduction in the efficiency of the polymerase enzyme leading to a replication rate of 3–15% that of wild type virus in in vitro assays [19,20]. The S282T variant either can pre-exist before treatment in some patients or may be selected during therapy, but its poor fitness does not allow this variant to expand to any significant degree. This is the reason why it is very infrequently found in patients who fail NA therapy, and why retreatment with NA for longer durations is feasible and can lead to SVR [21].

Another important requirement for any DAA to become a backbone in an IFN-free regimen is to have a potent antiviral activity, which is essential to achieve SVR and to overcome modest resistance. Ideally, this compound should also have a pangenotypic activity in order to be given in all HCV regimens. NA NS5B polymerase inhibitors, as a class, fulfil all these characteristics.

Among currently available or nearly available DAAs, the other molecule which fulfils nearly the same requirements is the second generation PI MK5172 (MSD, White house, USA). This newer PI has higher barriers to resistance and broader genotypic coverage than first generation PIs (although again not covering genotype 3 HCV) that make it a potentially good backbone candidate for HCV treatment [22].

Host targeting agents (HTAs) inhibit a host function necessary for HCV replication. Because they target the host, HTAs are usually considered to have a high barrier to resistance and a pangenotypic activity and therefore, can be used as a backbone in HCV treatment. Two classes of HTAs have been clinically developed so far, the cyclophilin inhibitors and miR-122 antagonists. Alisporivir (Novartis, Basel, Switzerland) is the cyclophilin inhibitor with the most advanced clinical development [23]. During the last two years it has been put on clinical hold due to a fatal case of acute pancreatitis that occurred in combination with PR. It is now back in development for all genotypes [24]. Alisporivir has demonstrated high barrier to resistance in IFN-free regimens in genotype 2 or 3 patients [23]. However, the antiviral potency is lower than that observed with DAAs. The miR-122 antagonist miravirsen (Santaris Pharma, Copenhagen, Denmark) has demonstrated a potent antiviral activity (reduction up to 3 logs IU/ml) after two weeks of intravenous infusions in genotype 1 patients [25]. However, there are some concerns about the hypothetic long-term hepatic effects of inhibiting miR-122 and the risk of steatohepatitis, fibrosis and hepatocellular carcinoma.

The other alternative targets for HCV specific therapy, such as HCV entry inhibitors or NS4B function inhibitors could theoretically have a pangenotypic activity with a good barrier to resistance. However, none of the HCV entry inhibitor candidates have moved into late clinical development, and they have demonstrated only mild antiviral potency. Among NS5B function inhibitors, silibinin is, up to now, the only compound that has been studied with encouraging results despite the possible occurrence of mutations in NS4B that confer partial resistance to silibinin in vitro [26].

In summary, in IFN-free regimens, a pangenotypic backbone appears to be necessary and NA NS5B polymerase inhibitors appear to be the best class of DAAs to fulfil this role.

2. Nucleotide analogues NS5B polymerase inhibitors: good candidates to act as backbones in IFN-free combinations

NAs bind to the NS5B active sites, causing chain termination and/or an increased number of errors when incorporated into a growing RNA chain. The NS5B's active site being well conserved, NAs tend to have a similar efficacy across all genotypes and present the highest barrier to resistance of all DAAs to date. In contrast, NNAs have shown a restricted spectrum of activity against the various HCV genotypes. They are mainly active against HCV GT-1 and present the lowest barrier to resistance. NS5B NAs appear, therefore, to be among the most promising pangenotypic drugs. Nucleosides are sugars bound to one of the bases used for DNA or RNA synthesis, while nucleotides are nucleosides with the addition of a phosphate group [26,27]. A vast majority of nucleotide analogues are prodrugs that are linked to a molecule that is cleaved mainly by hepatic enzymes to increase delivery of the nucleotide monophosphate to the hepatocyte. Within the cells, nucleotides or nucleosides need phosphorylation to be transformed into their active forms. HCV RdRp as a false substrate incorporates the triphosphate form during RNA replication leading to chain termination and inhibition of viral replication [28]. However, natural nucleotides are also required by the host cell for replication. Even if NAs are designed to serve as specific substrates for viral polymerase, they may also be incorporated by host polymerases and therefore lead to toxicity. This pattern was observed with fialuridine, with HBV NAs and with early HIV NAs (D4T, DDI) but up to now it has not been observed in HCV NAs.

However, other toxicities have been reported with some of the first HCV NAs. All guanosine NAs were discontinued during phase 2a due to gastrointestinal toxicities for valopicitabine, lymphopenia for R-1626, hepatotoxicity for PSI-938 and cardiac toxicity for BMS-986094.

Mericitabine is the only cytidine NA developed so far. In triple therapy for 24 weeks with ribavirin and danoprevir, a ritonavir boosted PI, mericitabine was shown to be moderately potent in genotype 1b naïve patients with 71% of SVR, and inefficient in genotype 1a naïve patients with 26% of SVR [29]. In quadruple therapy for 12 or 24 weeks with ribavirin, danoprevir and setrobuvir, a NS5B NNA, mericitabine was potent in genotype 1b patients with 96% of SVR, but less potent in genotype 1a patients [30]. Therefore, given the lower potency in genotype 1a patients, it is unlikely that mericitabine will play a major role in HCV therapy in the future.

Among the uridine NAs, sofosbuvir is the only drug approved by both FDA and EMA. VX-135 is another uridine NA in development. In combination with ribavirin VX-135 demonstrated viral potency in genotype 1 patients [31]. However, based on liver enzyme elevations seen at the dose of 400 mg in 3 out of 10 patients, the drug was placed on partial clinical hold by FDA limiting further studies to a maximal dose of 200 mg. In combination for 12 weeks with daclatasvir, an NS5A inhibitor, VX-135 at the dose of 200 mg daily was able to reach 91% of SVR in a small pilot study [32]. Other uridine NAs with good profiles that are actually in the pre-clinical stage are IDX-21437 or ACH-3422 [33].

Therefore, to date and for at least one or two years, sofosbuvir will remain the only NS5B NA available in clinical practice. Sofosbuvir is a prodrug of 2′deoxy-2′-fluoro-2′-C-methyluridine monophosphate, which must be phosphorylated twice after entering the hepatocyte [34]. The drug is absorbed intact through the gastrointestinal tract with no significant food effect and results in a high liver exposure. Sofosbuvir is largely excreted through the

kidney. Importantly, sofosbuvir does not interact with cytochrome P450 system or any other major drug metabolizing enzymes and therefore has no or few drug-drug interactions, allowing easier treatment in patients on other medications such as transplanted or co-infected patients. Sofosbuvir has so far been administered to more than 5000 patients, including patients with advanced cirrhosis, HIV co-infection, patients awaiting liver transplantation and patients with severe post-transplant recurrence, with a clean safety profile [35]. The efficacy and the safety of sofosbuvir have led to its rapid clinical development as a backbone of IFN-free DAA regimens.

3. Clinical data with sofosbuvir in IFN-free regimens

The clinical data on sofosbuvir as part of IFN-free regimens according to genotype and treatment status are summarized in Tables 1 and 2.

3.1. Genotype 1

3.1.1. Sofosbuvir plus ribavirin

This combination has been evaluated in genotype 1 patients in several small studies with conflicting and relatively disappointing results. In the initial ELECTRON study, sofosbuvir 400 mg daily with weight-based ribavirin was given to 25 naïve non-cirrhotic genotype 1 patients for 12 weeks. All patients suppressed virus on treatment and 84% achieved SVR [36]. In the next QUANTUM study, 38 naïve genotype 1 patients with mild fibrosis were randomized to receive 12 or 24 weeks of the same regimen. Overall SVR rate was 50% (53% for 12 weeks and 47% for 24 weeks) [37]. The discrepancy between the two studies may be related to a lower percentage of patients with favourable IL28B CC genotype in the QUANTUM study. In the SPARE study, sofosbuvir and ribavirin were given for 24 weeks with either a weight-based ribavirin dose or a lower 600 mg daily dose in a hard-to-treat population, mainly overweight African Americans with more advanced fibrosis. The study highlights the importance of the ribavirin dose when it is associated with sofosbuvir alone as the SVR rate was 68% in the weight-based group versus 48% in the low ribavirin dose group [38]. Moreover, relapse was more frequent among patients with advanced fibrosis and all cirrhotic patients relapsed. In the PHOTON-1 study, 114 naïve genotype 1 HIV/HVC co-infected patients were treated for 24 weeks with sofosbuvir and weight-based ribavirin. SVR rate was 76%. This may be partly explained by the baseline characteristics of the population with mainly white patients with mild fibrosis (5 patients had cirrhosis) and the high proportion (26%) of favourable IL28B CC genotype [39]. In a phase 2 open-label study in patients awaiting liver transplantation (LT), 61 cirrhotic patients with a Child Pugh score $\leq$7, with a median MELD score of 8 (6–14) received up to 48 weeks of sofosbuvir and weight-dosed ribavirin while on the waiting list before LT (median duration 17 weeks) [40]. 73% of the patients were genotype 1, 76% of the patients were IL28B non-CC and 75% of the patients had failed treatment on PR. Forty-four patients underwent LT and of these, 41 (93%) had HCV RNA < 25 IU/ml before LT. Of these, 39 patients reached 12 weeks of follow-up post transplantation and 64% achieved SVR. Safety and tolerance of this regimen were good. Most frequently reported adverse events were mild and only one patient discontinued treatment due to ribavirin-induced anaemia.

In treatment-experienced patients with failure to PR, the initial ELECTRON study demonstrated a disappointing 10% SVR rate in the ten patients who received sofosbuvir and weight-dosed ribavirin for 12 weeks [36]. However, in the post transplant study, 33 genotype 1 patients were treated for 24 weeks with sofosbuvir and ribavirin and 70% achieved SVR [41]. One hundred and five genotype 1 patients, who where non-responders or relapsers after a previous treatment with sofosbuvir or GS-0938 with or without ribavirin, were retreated with sofosbuvir and ribavirin for 24 weeks in the QUANTUM study and 65% achieved SVR [37].

In summary, the sofosbuvir - ribavirin combination in genotype 1 patients appears to be a suboptimal regimen, and should therefore be considered as an alternative approach for patients who cannot take PEG-IFN and when other DAAs are not available. The combination of sofosbuvir with another class of DAAs, either PIs or NS5A inhibitors, gives more impressive SVR results and should be preferred, when available, in genotype 1 patients.

3.1.2. Sofosbuvir plus protease inhibitors

The combination of sofosbuvir (400 mg daily) with the second-wave, first generation PI simeprevir (150 mg daily) with or without weight-dosed ribavirin for 12 or 24 weeks was evaluated in the COSMOS trial [42]. One hundred and sixty seven genotype 1 patients were treated. The study was divided into two cohorts: (1) 80 patients prior null responders to PR with fibrosis stage F0-2 and (2) 87 patients treatment naïve or prior null responders to PR with fibrosis stage F3-4.

Of the 39 treatment-naïve F3-4 patients, 95% achieved SVR, regardless of whether the regimen was given 12 or 24 weeks and whether it included ribavirin. Among prior null responders to PR, in cohort 1, the SVR rate with 12 or 24 weeks with or without ribavirin was similar and high across all groups (Table 1). In cohort 2, among the 47 prior null responders to PR patients with advanced fibrosis or cirrhosis the SVR rate was again high, over 90% across all groups (Table 1). SVR was similar regardless of whether the regimen was given for 12 or 24 weeks and whether it included ribavirin. Across both cohorts SVR was similar according to subtype, 95% in genotype 1b and 92% in genotype 1a. Moreover, regarding the influence of Q80K mutation at baseline on SVR rate in genotype 1a patients, 58 patients harboured this mutation at baseline across all groups and 88% (51/58) achieved SVR compared with 94% (68/72) in those without this mutation. Based on this study, 12 weeks of sofosbuvir and simeprevir without ribavirin appear to be a very efficacious regimen with a good safety profile in genotype 1 patients. Whether or not genotype 1a patients with baseline Q80K mutation should be treated with another combination with NS5A inhibitors remains an open issue.

3.1.3. Sofosbuvir plus NS5A inhibitors

The combination of sofosbuvir with NS5A inhibitors is a very attractive combination due to the potency and the pangenotypic activity of both molecules and the high barrier to resistance of NAs.

Sofosbuvir was initially evaluated in combination with daclatasvir (60 mg daily) with or without ribavirin for 12 or 24 weeks in 126 naïve genotype 1 patients with mainly mild fibrosis [43]. All patients treated 24 weeks achieved SVR. Among those treated 12 weeks, the SVR was 100% without ribavirin and 95% with ribavirin with no on-treatment breakthrough. This combination for 24 weeks was also evaluated in 41 patients with mild or moderate fibrosis who had failed prior triple therapy with either boceprevir or telaprevir. All patients achieved SVR.

These results were therefore confirmed when sofosbuvir was combined with ledipasvir (90 mg daily) in a fixed-dose combination (FDC) pill. The FDC regimen in genotype 1 naïve patients was initially evaluated with or without ribavirin for 12 or 8 weeks in the phase II study [44]. All patients achieved SVR in the FDC regimen with ribavirin for 8 weeks, while in both arms with FDC regimen without ribavirin for 8 or 12 weeks one patient relapsed, therefore 95% SVR was achieved. Similar results were obtained in treatment-experienced patients, who had failed triple therapy with PIs, treated

Table 1
Summary of clinical trial data with sofosbuvir in IFN-free regimens for genotype 1 patients.

Population	Study (Ref.)	N. patients	Treatment regimen	Duration (wk)	SVR12 (%)
Genotype 1 naïve	ELECTRON [36]	25	SOF + RBV	12	84%
	QUANTUM [37]	38	SOF + RBV	12 vs 24	12w: 53% 24w: 47%
	SPARE [38]	50	SOF + RBV WB or LDRBV	24	WB: 68% LD: 48%
	PHOTON [39] HIV + HCV	114	SOF + RBV	24	76%
	COSMOS [42] Cohort 2 F3/F4	39	SOF + SIM ± RBV	12 or 24	95% 12w = 24w
	AI1444-40 [43]	126	SOF + DCV ± RBV	12 or 24	12w: SOF/DCV: 98% SOF/DCV/RBV: 95% 24w: SOF/DCV: 100% SF/DCV/RBV: 100%
	ELECTRON [51]	25	SOF + LDV + RBV	6	68%
	LONESTAR [44]	60	SOF + LDV ± RBV	8 or 12	8w SOF/LDV: 95% 8w SOF/LDV/RBV: 100% 12w SOF/LDV: 95%
	ION-1 [45]	865	SOF + LDV ± RBV	12 or 24	12w: SOF/LDV: 99% SOF/LDV/RBV: 97% 24w: SOF/LDV: 98% SOF/LDV/RBV: 99%
	ION-3 [46]	647	SOF + LDV ± RBV	8 or 12	8w: SOF/LDV: 94% 8w: SOF/LDV/RBV: 93% 12w: SOF/LDV: 95%
	ELECTRON-2 [21]	20 cirrhotic CPT B	SOF + LDV	12	65%
	ERADICATE [48] HIV + HCV	50	SOF + LDV	12	100% interim results
	SYNERGY [52]	60	SOF + LDV ± GS-9669 (NNI) or GS-9451 (PI)	6 or 12	12w: SOF/LDV: 100% 6w: SOF/LDV/9669: 90% 6w:SOF/LDV/9451:100%
	New combination [50]	55	SOF + GS-5816 (25 or 100 mg)	12	25 mg: 96% 100 mg: 100%
Genotype 1 treatment-experienced	ELECTRON [36]	10	SOF + RBV	12	10%
	QUANTUM [37] NR to DAA regimen including SOF or GS-0938 ± RBV	105	SOF + RBV	24	65%
	Post transplant study [41]	33	SOF + RBV	24	70%
	COSMOS [42] Cohort 1 F0/F2	80	SOF + SIM ± RBV	12 or 24	12w SOF/SIM: 93% SOF/SIM/RBV: 96% 24w SOF/SIM: 93% SOF/SIM/RBV: 79%
	COSMOS [42] Cohort 2 F3/F4	47	SOF + SIM ± RBV	12 or 24	12w: SOF/SIM: 93% SOF/SIM/RBV: 93% 24w: SOF/SIM: 100% SOF/SIM/RBV: 93%
	A1444-40 [43] PI failure	41	SOF + DCV ± RBV	24	SOF/DCV: 100% SOF/DCV/RBV: 100%
	LONESTAR [44] PI failure	40	SOF + LDV ± RBV	12	SOF/LDV: 95% SOF/LDV/RBV: 100%
	ELECTRON [51]	70	SOF + LDV ± RBV or GS-9669 (NNI)	12	F4: SOF/LDV: 70% F4: SOF/LDV/RBV: 100% F3/4: SOF/LDV/RBV: 100% SOF/LDV/9669: 100%
	ION-2 [47] Including PI failure	440 (231PI failure)	SOF + LDV ± RBV	12 or 24	12w: SOF/LDV: 94% SOF/LDV/RBV: 96% 24w: SOF/LDV: 99% SOF/LDV/RBV: 99%
	ELECTRON2 [21] SOF failure	19	SOF + LDV + RBV	12	100%
	SYNERGY [49] SOF/RBV relapsers	14	SOF + LDV	12	100%

SOF, sofosbuvir; RBV, ribavirin; WB, weight-based ribavirin dose; LDRBV, low dose ribavirin; SIM, simeprevir; DCV, daclatasvir; LDV, ledipasvir (NS5A I); GS-5816 (new NS5A I. second generation); PR, peg-interferon plus ribavirin.

with FDC regimen with (100% SVR) or without ribavirin (95% SVR) for 12 weeks. In order to clarify the duration of treatment and the need for ribavirin with the FDC regimen, three large phases III trial were conducted. ION-1 and ION-3 studies were conducted in 1512 naïve genotype 1 patients. In ION-1 study, 865 patients were randomized to receive FDC regimen with or without ribavirin for 12 or 24 weeks [45]. The rate of SVR in all treatment groups was 97% or higher regardless of whether the regimen was given for 12 or

Table 2
Summary of clinical trial data with sofosbuvir in IFN-free regimens for genotypes 2–6 patients.

Population	Study (Ref.)	N. patients	Treatment regimen	Duration (wk)	SVR12 (%)
Genotype 2 naïve	ELECTRON [36]	4	SOF + RBV	12	4/4: 100%
	FISSION [53]	137	SOF + RBV 12w vs. PR 24w	12 24	SOF/RBV: 97% PR: 78%
	POSITRON [54]	109	SOF + RBV	12	93%
	VALENCE [55]	32	SOF + RBV	12	97%
	PHOTON [39]HIV + HCV	26	SOF + RBV	12	88%
	AI1444-40 [43]	26	SOF + DCV ± RBV	24	96%
	New combination [50]	21	SOF + GS-5816 (25 or 100 mg)	12	25 mg: 91% 100 mg: 100%
Genotype 2 treatment-experienced	FUSION [54]	68	SOF + RBV	12 or 16	12w: 86% F4: 60% 16w: 94% F4: 78%
	PHOTON HIV + HCV	24	SOF + RBV	12	92%
	VALENCE [55]	41	SOF + RBV	12	90%, F4: 78%
Genotype 3 naïve	ELECTRON [36]	6	SOF + RBV	12	6/6: 100%
	FISSION [53]	359	SOF + RBV 12w vs. PR 24w	12 24	SOF/RBV: 56% PR: 62%
	POSITRON [54]	98	SOF + RBV	12	61%
	VALENCE [55]	105	SOF + RBV	24	94%, F4: 92%
	PHOTON [39]HIV + HCV	42	SOF + RBV	12	67%
	AI1444-40 [43]	18	SOF + DCV ± RBV	24	94%
	ELECTRON-2 [21]	51	SOF + LDV ± RBV	12	SOF/LDV: 64% SOF/LDV/RBV: 100%
	New combination [50]	54	SOF + GS-5816 (25 or 100 mg)	12	25 mg: 93% 100 mg: 93%
Genotype 3 treatment-experienced	FUSION [54]	127	SOF + RBV	12 or 16	12w: 30% F4: 19% 16w: 62% F4: 61%
	PHOTON HIV + HCV	17	SOF + RBV	12	94%
	VALENCE [55]	145	SOF + RBV	24	79%, F4: 62%
Genotype 4 naïve	HCV GT-4 [58]	28	SOF + RBV	12 or 24	12w: 79% 24w: 100%
	New combination [50]	14	SOF + GS-5816 (25 or 100 mg)	12	25 mg: 100% 100 mg: 86%
Genotype 4 treatment-experienced	HCV GT-4 [58]	32	SOF + RBV	12 or 24	12w: 59% 24w: 87%
Genotype 5 naïve	New combination [50]	1	SOF + GS-5816 (25 mg)	12	1/1: 100%
Genotype 6 naïve	New combination [50]	9	SOF + GS-5816 (25 or 100 mg)	12	25 mg: 100% 100 mg: 100%

SOF, sofosbuvir; RBV, ribavirin; SIM, simeprevir; DCV, daclatasvir; LDV, ledipasvir (NS5A I); GS-5816 (new NS5A I. second generation); PR, peg-interferon plus ribavirin.

24 weeks and whether it included ribavirin. The rates of treatment discontinuation were higher in the groups treated for 24 weeks than in the groups treated for 12 weeks. Similarly the rates of side effects were higher in the groups that received ribavirin than in the corresponding group that did not. Moreover, SVR rates were uniform, regardless of the baseline characteristic of the patients. In particular, the presence of cirrhosis had no marked effects on SVR rate (97–100%) and safety profile. The ION-1 study showed that 12 weeks FDC is highly effective in genotype 1 naïve patients without any additional benefit in extending treatment duration or addition of ribavirin.

In the ION-3 study 647 naïve-genotype 1 patients without cirrhosis were randomized to receive FDC regimen with or without ribavirin for 8 weeks or FDC regimen for 12 weeks [46]. The rates of SVR in the three treatment groups were high, over 90% (94% FDC 8 weeks, 93% FDC + ribavirin 8 weeks and 95% in FDC 12 weeks). The results of non-inferiority analysis suggested that adding ribavirin to the 8 weeks FDC regimen or extending duration from 8 to 12 weeks did not result in improved SVR rates. SVR rates were uniform regardless of the baseline characteristics historically associated with a poor response to PR. Although relapse was more common among patients who received 8 weeks of treatment (20 vs. 3), no baseline characteristics or on-treatment variables could be identified associated with relapse. This study suggests that only 8 weeks of FDC may be sufficient for the treatment of naïve non-cirrhotic genotype 1 patients.

In the ION-2 study, 440 treatment-experienced genotype 1 patients, including 231 patients who had failed triple therapy with PIs, were randomized to receive FDC regimen with or without ribavirin for 12 or 24 weeks [47]. Similarly to ION-1 study, the rates of SVR in all treatment arms were between 94 and 99%. They were similar with widely overlapping confidence intervals regardless of treatment duration or use of ribavirin. However, this study was not powered to compare responses to regimens with or without ribavirin or to 12 or 24 weeks of treatment. In cirrhotic patients SVR rate was modestly lower in patients treated for 12 weeks (86% FDC and 82% FDC plus ribavirin) than in those without cirrhosis (95 and 100% respectively), whereas in the 24 weeks treatment groups, SVR rates were similar in patients with cirrhosis (99%) and in those without cirrhosis (100%). No baseline factors or on-treatment viral kinetics during the first 2 weeks of treatment was predictive of relapse in patients with cirrhosis treated for 12 weeks. Overall these results suggest that in treatment experienced patients, non-cirrhotic patients may benefit from 12 weeks of FDC without additional benefit of extending treatment duration or addition of ribavirin, whereas in cirrhotic

patients 24 weeks of FDC may be more suitable in order to maximize SVR.

FDC regimen was also evaluated in fifty naïve HIV/HCV genotype 1 patients leading to SVR in all patients treated for 12 weeks so far [48]. In advanced cirrhotic patients CPT B the same regimen led to 65% of SVR suggesting that longer treatment duration is suitable in this situation [21]. In patients who previously failed or relapsed to sofosbuvir containing regimen, all patients achieved SVR with FDC regimen with or without ribavirin for 12 weeks [21,49].

Sofosbuvir was recently associated in a phase 2 study with a new, very potent and pan genotypic NS5A inhibitor (GS-5816). Preliminary results showed that at the dose of 100 mg of GS-5816 combined with sofosbuvir for 12 weeks all genotype 1 naïve patients achieved SVR [50].

3.1.4. Sofosbuvir in combination with multiple DAAs

The rationale for such a combination is to maximize, if possible, SVR rate in a difficult-to-treat population or to try to shorten treatment duration. In the ELECTRON study, seventy treatment-experienced patients with advanced fibrosis or cirrhosis were randomized to receive FDC with or without ribavirin or FDC plus GS-9669, a NS5B NNI, for 12 weeks [51]. SVR rate was 70% among the cirrhotic patients treated with FDC, although SVR was achieved in all patients treated either with FDC plus ribavirin or GS-9669. The SYNERGY phase II study evaluated FDC in combination with GS-9669 or GS-9451, a second wave PI for 6 weeks in naïve genotype 1 patients [52]. All twenty patients treated with FDC plus GS-9651 achieved SVR and 18/20 (90%) achieved SVR in the group treated with FDC plus GS-9669. These preliminary data suggest that adding other potent DAAs to the FDC could either maximize the virological response in most difficult-to-treat patients or allow the shortening of treatment duration.

3.2. Genotype 2

SVR in genotype 2 patients differs markedly to that in genotype 3 patients with PR regimen but the difference is even more obvious with IFN-free DAA regimens. Therefore, SVR data need to be analysed separately.

3.2.1. Sofosbuvir plus ribavirin

After the initial ELECTRON study, in which all four naïve genotype 2 patients achieved SVR [36], three large phase III trials (FISSION, POSITRON, VALENCE) confirmed that in naïve genotype 2 patients this regimen for 12 weeks achieved SVR in more than 93% of the patients (Table 2) [53–55]. Moreover, the randomized controlled FISSION study demonstrated that sofosbuvir plus ribavirin for 12 weeks was significantly superior compared to the standard PR regimen for 24 weeks [53]. Across the three studies, thirty naïve cirrhotic patients were treated and 28 (93%) achieve SVR with a 12 week regimen. Based on the results of these trials, both FDA and EMA have approved sofosbuvir and ribavirin for 12 weeks in all genotype 2 naïve patients. The same results were obtained in the HIV/HCV co-infected trial in which SVR rate was 88% in genotype 2 patients [39].

In the FUSION study, sixty-eight genotype 2 patients who failed prior PR regimen were randomized to receive sofosbuvir plus ribavirin for 12 or 16 weeks [54]. Among the forty-nine non-cirrhotic patients SVR rate was similar in both arms: 96% for 12 weeks and 100% for 16 weeks respectively. On the other hand, among the 19 cirrhotic patients, the SVR rate was 60% for 12 weeks and 78% for 16 weeks, suggesting that longer treatment duration may improve SVR. However, the small number of patients limits the possibility of drawing a strong conclusion, moreover, in the VALENCE study, in which genotype 2 patients were treated for 12 weeks, the SVR rate among the nine treatment-experienced patients with cirrhosis was 78% [55].

3.2.2. Sofosbuvir plus NS5A inhibitors

Sofosbuvir was evaluated in combination with daclatasvir (60 mg daily) with or without ribavirin in 26 naïve genotype 2 patients, four of whom had cirrhosis [43]. SVR rate was 96%. Ribavirin did not seem to necessary to the achievement of SVR, however, the number of patients is too small to draw any significant conclusion. No data are available for genotype 2 patients with the combination of sofosbuvir plus ledipasvir.

Sofosbuvir was also evaluated in combination with GS-5816 in 21 genotype 2 naïve-patients [50]. All patients but one (who died during follow-up) achieved SVR.

In conclusion, in genotype 2 patients either treatment-naïve any fibrosis stage or treatment-experienced without cirrhosis, sofosbuvir plus ribavirin for 12 weeks achieved a very high SVR and is the recommended regimen worldwide. For treatment-experienced patients with cirrhosis, this regimen is suboptimal and treatment may be extended up to 16 weeks or longer [56]. Another option, that needs to be studied, is to use the combination of sofosbuvir plus NS5A inhibitors (daclatasvir or others) for 12 or 24 weeks.

3.3. Genotype 3

Genotype 3 patients appear to be the most difficult to cure population in IFN-free regimen with the three drug currently available [56].

3.3.1. Sofosbuvir plus ribavirin

After the initial ELECTRON study, in which all six naïve genotype 3 patients achieved SVR [36], three large phase III trials (FISSION, POSITRON, VALENCE) were conducted in naïve genotype 3 patients (Table 2) [53–55]. The randomized controlled FISSION study conducted among three hundred and fifty-nine naïve patients demonstrated similar SVR rates in patients treated with sofosbuvir plus ribavirin for 12 weeks compared to the standard PR regimen for 24 weeks, 56% and 62% respectively [53]. In the POSITRON study, ninety eight naïve genotype 3 patients achieved an SVR rate of 61% [54] and similar results were found in the HIV/HCV co-infected study with a 67% SVR rate [39]. Across the two studies, fifty-two naïve cirrhotic patients were treated and sixteen (31%) achieved SVR with a 12 week regimen. Therefore, the VALENCE study was conducted in one hundred and five naïve patients treated with sofosbuvir and ribavirin for 24 weeks [55]. 94% of the non-cirrhotic patients and 92% of the thirteen cirrhotic patients achieved SVR. Based on the results of these trials, both FDA and EMA have approved sofosbuvir and ribavirin for 24 weeks in all genotype 3 naïve patients.

The randomized FUSION study conducted among 127 genotype 3 patients who failed prior PR regimen demonstrated a poor SVR rate of 30% for those treated for 12 weeks and 62% for those treated for 16 weeks [54]. Treatment duration was extended to 24 weeks in the VALENCE study in one hundred and forty-five patients. SVR was achieved in 79% of the patients: the rate was 87% in non-cirrhotic patients and 62% in the forty-seven cirrhotic patients [55].

3.3.2. Sofosbuvir plus NS5A inhibitors

Sofosbuvir was evaluated in combination with daclatasvir (60 mg daily) with or without ribavirin in eighteen naïve genotype 3 patients, two of whom had cirrhosis [43]. SVR rate was

94%. Ribavirin did not seem to add anything towards SVR; however, the number of patients was too small to draw any significant conclusion.

Sofosbuvir plus ledipasvir in FDC with or without ribavirin for 12 weeks was evaluated in fifty-one naïve genotype 3 patients including 8 patients with cirrhosis. 64% of patients treated with sofosbuvir and ledipasvir achieved SVR, whereas all those treated with FDC plus ribavirin achieved SVR [21].

Sofosbuvir was also evaluated in combination with GS-5816 (25 or 100 mg daily) in fifty-four genotype 3 naïve patients [50]. 93% of these patients achieved SVR.

In conclusion, in genotype 3 patients either treatment-naïve any fibrosis stage or treatment-experienced without cirrhosis, sofosbuvir plus ribavirin for 24 weeks achieved a very high SVR rate and is the recommended regimen worldwide. For treatment-experienced patients this regimen is suboptimal and other options need to be studied e.g. a combination of sofosbuvir with daclatasvir or other NS5A inhibitor such as ledipasvir, or others, for 12 or 24 weeks. Ongoing studies will hopefully discover the optimal treatment for these patients. Another option, already explored in an observational study in patients who relapsed after sofosbuvir and ribavirin, is treatment with sofosbuvir and PR for 12 weeks, which was shown to achieve SVR in 93% of non-cirrhotic patients and 88% of cirrhotic genotype 3 patients [57].

3.4. Genotype 4

Few data are available for this population. In a small study, conducted in Egyptian patients treated in the USA with sofosbuvir and ribavirin for 12 or 24 weeks, SVR was achieved in 79% of the fourteen treatment-naïve patients treated for 12 weeks and in all the fourteen treatment-naïve patients treated for 24 weeks [58]. Among treatment-experienced patients, 59% of the seventeen patients treated 12 weeks and 87% of the fifteen patients treated for 24 weeks achieved SVR [58]. Moreover, all of the seven cirrhotic patients treated 24 weeks achieved SVR.

Fourteen treatment-naïve patients were treated with sofosbuvir plus GS-5816 (25 or 100 mg daily) for 12 weeks in a small pilot trial [50]. All, except one patient lost to follow-up, achieved SVR.

Based on this small dataset sofosbuvir plus ribavirin for 24 weeks may be recommended in genotype 4 patients. However, other combinations with sofosbuvir and daclatasvir or simeprevir need to be studied due to the efficacy of these drugs for genotype 4 and ongoing studies will again clarify the optimal management of this population.

3.5. Genotypes 5 and 6

We have few data for this population with sofosbuvir and PR for 12 weeks, and there is a lack of data regarding sofosbuvir plus ribavirin in this population. In the NEUTRINO study, all seven genotype 5 or 6 treatment-naïve patients treated with sofosbuvir and PR for 12 weeks achieved SVR [53]. In a small study one genotype 5 and nine genotype 6 treatment-naïve patients were treated with sofosbuvir plus GS-5816 for 12 weeks and all achieved SVR [50].

4. Resistance

Resistance does not appear to be a significant issue with sofosbuvir-containing regimens due to the high barrier to resistance of the molecule. In the LONESTAR study, one patient who relapsed after 8 weeks of FDC was found to harbour both an NS5A resistant mutation (L31M and Y93H) and the S282T signature sofosbuvir resistant mutation [44]. The L31M mutation was already present prior to commencing therapy. Due to its poor fitness the frequency of the S282T mutant decreased within two weeks. Retreatment of this patient with FDC plus ribavirin for 24 weeks achieved SVR. Since this initial observation, at least eighty-five patients who have relapsed with a sofosbuvir-containing regimen have been retreated with an IFN free sofosbuvir-containing regimen achieving a high rate of SVR [21,57]. In these two studies, the S282T resistant mutant was not detected, either due to the poor fitness of the variant or a lack of sensitivity of the methods used to detect the variant. Anyhow, of the nineteen genotype 1 patients who relapsed with sofosbuvir plus ribavirin for 12 weeks ($n = 10$), FDC for 6 weeks ($n = 8$) or sofosbuvir plus ribavirin and GS-9669 for 12 weeks ($n = 1$), all achieved SVR after 12 weeks of FDC with ribavirin [21]. In another observational study, sixty-six genotype 2 or 3 patients who relapsed after sofosbuvir and ribavirin were retreated with either sofosbuvir plus ribavirin for 24 weeks ($n = 40$) or sofosbuvir plus PR for 12 weeks ($n = 26$) [57]. 63% of the patients treated with sofosbuvir and ribavirin and 92% of those treated with sofosbuvir and PR achieved SVR. All these data demonstrate that a sofosbuvir resistant mutant is really not a significant issue as long as we can retreat patients with a combination in which sofosbuvir is associated with any DAA with activity against the S282T resistant mutant.

5. Factors predicting failure for sofosbuvir containing treatments

The high success rates achieved with sofosbuvir make identification of predictive factors of failure rather difficult. For the combination of sofosbuvir plus ribavirin the lower SVR rate observed in genotype 3 patients showed that previous treatment failure on PR, cirrhosis and slow viral decline during the first two weeks of treatment are associated with treatment failure on sofosbuvir [55]. Once a second DAA is added to sofosbuvir, even baseline characteristics such as cirrhosis become less and less important. In the ION-2 study, only cirrhosis was predictive of failure for the 12 week regimen, but all cirrhotic patients achieved SVR with FDC for 24 weeks.

6. Conclusion

The launch of sofosbuvir is a major advance in HCV treatment. The potency, high barrier to resistance, pangenotypic activity, once-daily dosage, good safety profile and the limited drug-drug interactions make this compound an ideal backbone for IFN-free regimens. The data already collected has demonstrated that sofosbuvir plus ribavirin treatment in genotype 2, 3 and 4 allows the achievement of SVR at least in 90% of the patients. Sofosbuvir in combination with either NS5A inhibitors (daclatasvir or ledipasvir) or PIs (simeprevir) achieves SVR in more than 95% of genotype 1 patients. Hopefully ongoing studies will fill the remaining gap for treatment-experienced genotype 3 patients with DAA combinations. Moreover, shorter treatment duration (down to 6 weeks) becomes possible using the combination of sofosbuvir with multiple DAAs. Compliance to drug regimens will be a major issue if we want to avoid relapse. However, at the current price, treatment with DAAs, including sofosbuvir, will not be a viable option for many HCV infected people living in countries with strong economic constraints. Therefore, all efforts should be made to reduce the cost of such therapies so as to be able to extend treatment to the greatest number of patients.

Conflict of interest
None declared.

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